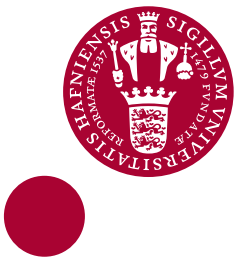

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ORIGINAL ARTICLE

The association between plasma miR-122-5p release pattern at admission and all-cause mortality or shock after out-of-hospital cardiac arrest

Patrik Gilje[a#], Martin Frydland[b], John Bro-Jeppesen[b], Josef Dankiewicz[c], Hans Friberg[c], Malin Rundgren[c], Yvan Devaux[d], Pascal Stammet[e], Mariam Al-Mashat[f], Jonas Jögi[f], Jesper Kjaergaard[b], Christian Hassager[b] and David Erlinge[a]

[a]Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden; [b]The Heart Centre, Department of Cardiology, Copenhagen University Hospital, Copenhagen, Denmark; [c]Department of Intensive and Perioperative Care, Clinical Sciences, Lund University, Lund, Sweden; [d]Cardiovascular Research Unit, Luxembourg Institute of Health, Luxembourg, Luxembourg; [e]The Medical Department, National Rescue Services, Luxembourg, Luxembourg; [f]Department of Clinical Physiology, Clinical Sciences, Lund University, Lund, Sweden

ABSTRACT

Background: Data suggests that the plasma levels of the liver-specific miR-122-5p might both be a marker of cardiogenic shock and a prognostic marker of out-of-hospital cardiac arrest (OHCA). Our aim was to characterize plasma miR-122-5p at admission after OHCA and to assess the association between miR-122-5p and relevant clinical factors such all-cause mortality and shock at admission after OHCA.

Methods: In the pilot trial, 10 survivors after OHCA were compared to 10 age- and sex-matched controls. In the main trial, 167 unconscious survivors of OHCA from the Targeted Temperature Management (TTM) trial were included.

Results: In the pilot trial, plasma miR-122-5p at admission after OHCA was 400-fold elevated compared to controls. In the main trial, plasma miR-122-5p at admission was independently associated with lactate and bystander cardiopulmonary resuscitation. miR-122-5p at admission was not associated with shock at admission ($p = 0.14$) or all-cause mortality ($p = 0.35$). Target temperature (33 °C vs 36 °C) was not associated with miR-122-5p levels at any time point.

Conclusions: After OHCA, miR-122-5p demonstrated a marked acute increase in plasma and was independently associated with lactate and bystander resuscitation. However, miR-122-5p at admission was not associated with all-cause mortality or shock at admission.

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Plasma microRNA; cardiac arrest; outcome; shock; lactate; bystander CPR

Introduction

Sudden out-of-hospital cardiac arrest (OHCA) is a cause of substantial mortality and morbidity (Dragancea *et al.* 2013). After return of spontaneous circulation, the post cardiac arrest syndrome ensues which is characterized by systemic inflammation, ischemia/reperfusion injury and organ dysfunction (Nolan *et al.* 2008). Hypoxic hepatitis occurs in 3–18% of OHCA-patients and is associated with increased intensive care unit mortality (Champigneulle *et al.* 2016). In the clinic, liver injury is usually detected by analyzing plasma levels of alanine aminotransferase (ALT) and an ALT-elevation above three times the upper limit of the normal range is a useful indicator of liver damage with high sensitivity and specificity (Senior 2012).

MicroRNAs (miRNAs) are short (18–23 nucleotides), non-coding RNAs that have a central role in regulating translation and degradation of messenger RNAs (mRNAs) inside the cell (Ha and Kim 2014). In addition, miRNAs are abundant in the blood, where they are protected from degradation by their association with proteins or extracellular vesicles (Arroyo *et al.* 2011). As some miRNAs also have a high degree of tissue specificity and due to their stability during storage and handling, miRNAs are potential diagnostic and prognostic biomarkers (Fichtlscherer *et al.* 2011).miR-122-5p is the most abundant miRNA in the human liver (Jopling 2012, Ludwig *et al.* 2016). However, miR-122-5p is largely absent in other organs including the brain and is regarded as liver-specific (Jopling 2012). miR-122-5p is vital for the regulation of lipid metabolism and cellular proliferation and has been associated with hepatitis and the development of hepatocellular carcinoma (Hsu *et al.* 2012). In plasma, miR-122-5p is a well-documented marker of both acute and chronic liver injury. In response to injury, blood levels of miR-122-5p seem to increase before aminotransferases, the most common clinical marker of active liver necrosis (Ward *et al.* 2014).

Recently, low levels of plasma miR-122-5p at 48 h after OHCA was shown to be an independent predictor of poor

CONTACT Patrik Gilje Giljepatrik.gilje@med.lu.se Department of Cardiology, Clinical Sciences, Lund University, Lund, Sweden
Supplemental data for this article can be accessed here.
[#]Patrik Gilje is responsible for statistical design/analysis.

Table 1. Patient characteristics.

	Pilot trial ($n = 10$)	Main trial ($n = 167$)	p-value
Age (years)	73	62	<0.05
Sex (female)	5/10 (50%)	21/167 (13%)	<0.01
Out-of-hospital CA	9/10 (90%)	167/167 (100%)	0.06
Bystander CPR (Yes)	6/10 (60%)	133/167 (80%)	0.23
Time CA to ROSC (min)	20 (12;28)	23 (14;30)	0.49
First rhythm (VT/VF)	8/10 (80%)	146/167 (87%)	0.61
Alive 180 days after CA (yes)	7/10 (70%)	109/167 (65%)	1.00
Shock at admission (yes)	–	17/167 (10%)	–
MAP at admission (mm Hg)	–	71 (65;80)	–
Creatinine at admission (mg/dl)	–	97 (82;116)	–
Lactate at admission (mmol/l)	–	7.5 (3.7;11.0)	–
Heart rate at admission (bpm)	–	72 (61;85)	–
LVIDD at admission (cm)	–	5.4 (5.9;4.8)	–

CA: cardiac arrest; CPR: cardiopulmonary resuscitation; ROSC: return of spontaneous circulation; VT: ventricular tachycardia; VF: ventricular fibrillation; MAP: mean arterial pressure; LVIDD: left ventricular internal diameter end diastole.

neurological outcome and all-cause mortality after OHCA. This was notable since previous studies have found high plasma levels of miR-122-5p during cardiogenic shock in patients and in pigs (Andersson *et al.* 2012, Cortez-Dias *et al.* 2016). Moreover, plasma levels of miR-122-5p during resuscitation for OHCA were higher among patients who died compared to survivors (Wander *et al.* 2016). Plasma levels of miR-122-5p after OHCA seem to fall between 24 h and 72 h after OHCA but the timeframe between resuscitation and 24 h after OHCA has not been evaluated (Devaux *et al.* 2017).

The aim of this study was to characterize plasma miR-122-5p after OHCA. With regards to the available evidence, we hypothesized that miR-122-5p would be elevated in survivors from OHCA at admission compared to matched controls. Furthermore, we aimed at assessing the association between miR-122-5p at admission and relevant clinical factors such as ALT, lactate, bystander CPR, targeted temperature management, hemodynamic/echocardiographic parameters and shock at admission.

Clinical significance

- Plasma miR-122-5p at 48 h after OHCA is an independent predictor of neurological outcome and all-cause mortality.
- Plasma miR-122-5p is elevated during cardiogenic shock in patients and in pigs.
- In the present study, plasma miR-122-5p at admission after OHCA was not associated with all-cause mortality, target temperature or shock at admission.

Methods

Pilot trial

In the pilot trial, 10 randomly selected patients from a separate OHCA cohort were included (Gilje *et al.* 2014). These were compared to a sex- and age-matched control group consisting of 10 outpatients undergoing myocardial perfusion scans due to suspicion of angina pectoris (5 women and 5 men in each group, median age 72 years in the control group and 73 years in the patient group; $p =$ not significant). The patients in the pilot trial were not included in the main trial and a comparison between the patients included in the two trials can be found in Table 1. For details about the miRNA-extraction in the pilot trial, see Supplementary file 1.

Main trial

Patients

The patients in the main trial originate from unconscious patients admitted after OHCA of presumed cardiac cause and were originally the Danish patients included in the Targeted Temperature Management (TTM) trial (Nielsen *et al.* 2013). Details about inclusion criterions can be found in Supplementary file 1.

Samples and clinical variables

Blood samples were obtained at admission followed by samples at 24, 48 and 72 h after return of spontaneous circulation (ROSC). In the univariate models, lactate at admission, LVIDD at admission, age, MAP, Creatinine admission, Time to ROSC, HR at admission, central venous pressure (CVP) at admission, first rhythm, target temperature, shock at admission, sex, bystander CPR, cardiac output at admission, LVEF at admission, initial temperature and high-sensitivity Troponin T at 48 h after OHCA were included. Missing values were replaced by multiple imputation. In the multiple linear regression and the logistic regression models, the variables that were deemed to be the most clinically and scientifically relevant were included. No patients were lost to follow up.

Biomarker analysis

Only miR-122-5p was analyzed in the current project and we did not perform any multiple testing of other miRNAs. RNA-extraction, cDNA-synthesis and quantitative PCR were performed by Exiqon Services, Denmark. Normalization was performed by using the average of the miRNAs that were detected in all samples and most stably expressed. For this purpose, hsa-miR23a-3p and hsa-miR-103a-3p were selected by the Normfinder software (Aarhus, Denmark). For details about the miRNA-extraction, see Supplementary file 1. ALT was analyzed according to the routine methods at the Copenhagen University Hospital and expressed as international units IU/litre.

Mortality and shock

All-cause mortality was assessed at 180 days after cardiac arrest. Cause of death was assessed by the treating physician. A subgroup was pre-specified based on the presence of shock at admission. Shock at admission was defined as a systolic blood pressure of <90 mmHg for >30 min or the need of supportive measures to maintain a blood pressure ≥90 mmHg and/or clinical signs of end-organ hypoperfusion (cool extremities, urine output of <30 ml/h).

Ethics approval and consent to participate

The samples in the pilot trial were analyzed in concordance with the approval of Regional Ethical Review Board at Lund University (411/2004 and 223/2008). Informed consent was sought from the patient's kin or retrospectively from the patient.

The samples in the main trial were collected as a part of the TTM trial (Nielsen *et al.* 2013). This protocol was approved by the ethics committee of Copenhagen University. Eligible patients were unconscious and unable to give informed consent in the acute setting. Randomization was justified before informed consent could be obtained according to the declaration of Helsinki Section 2.5. Patients regaining consciousness were asked for informed consent.

Statistics

Pilot trial

The Wilcoxon matched-pairs signed rank test was used for comparisons between paired groups. Comparisons between non-paired groups were performed using the Mann–Whitney test.

Main trial

Data are presented as medians, interquartile range, counts and proportions (%). Due to skewed distributions, miR-122-5p was log2-transformed prior to analysis. Missing data was handled with 10-fold multiple imputation (MCMC procedure). Continuous variables with normal distribution were compared using ANOVA. In order to compare pooled data from multiple imputation datasets, non-parametric continuous data were log-transformed before ANOVA analysis. Differences between repeated measurements of parametric groups were assessed using repeated measures of ANOVA with the Sidak correction. Pearson's chi Square test and Fisher's test was used for categorical data. Correlations between continuous data were assessed using Pearson's and Spearman correlation coefficients for parametric and non-parametric data, respectively. Associations between miR-122-5p and other parameters were investigated by multiple linear regression and logistic regression analysis. As the proportional hazard assumption was not fulfilled, logistic regression rather than Cox regression was performed. miR-122-5p at admission was log2-transformed before being entered as an independent variable in the logistic regression model. A *p*-value <0.05 was considered significant. IBM SPSS Statistics 22 (Foster City, USA) and GraphPad Prism 6 (La Jolla, USA) were used for the analyses.

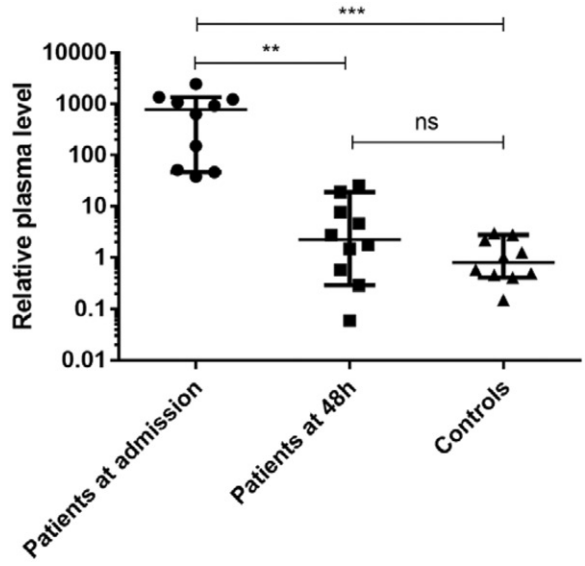

Figure 1. At admission, patients in the pilot trial had a 404-fold elevation of the median plasma level of miR-122-5p compared to controls ($p < 0.001$). (The lines represents medians and the 95% CI, **=$p \leq 0.01$, ***=$p \leq 0.001$, ns = not significant).

Results

Pilot trial

In the pilot trial, 10 survivors of OHCA were included and compared to 10 sex- and age-matched controls. At admission, the median plasma level of miR-122-5p was 404-fold elevated in OHCA-patients compared to controls ($p < 0.001$). At 48 h after OHCA there was no significant difference between patients and controls (Figure 1).

Main trial

In total, 171 patients were eligible for analysis. Two patients were excluded since blood samples were not available. Two patients were considered as outliers due to miR-122-5p levels deviating more than four standard deviations, and were excluded. Hence, 167 patients were included. Patient characteristics and a comparison to the pilot trial cohort can be found in Table 1. A patient flow diagram of the main trial is presented in Figure 2. One hundred and nine patients (65%) were alive at 180 days after OHCA.

The cohort in the main trial was younger and had more males compared to the pilot trial cohort. miR-122-5p was available for 161 patients (96%) at admission, 151 patients (90%) at 24 h, 145 patients (87%) at 48 h and 140 patients (84%) at 72 h. With regard to sex, OHCA, bystander CPR, first rhythm, alive at 180 days, shock at admission, time to ROSC, target temperature and age, no data was missing. For the other variables, the missing data were as follows: MAP at admission: 10%; creatinine at admission: 2%; lactate at admission: 17%; LVIDD at admission: 15%; CO at admission: 21%; CVP at admission: 21%; LVEF at admission: 21%;

hs-Troponin-T: 8%; initial temperature: 2%; and HR at admission: 4%.

Kinetics of circulating miR-122-5p following OHCA

As in the pilot trial, miR-122-5p peaked at admission and then declined before reaching a plateau level at 48 h (Figure 3(a)). The median/mean plasma level of miR-122-5p was 57-fold/140-fold elevated at admission compared to 72 h after OHCA ($p < 0.001$).

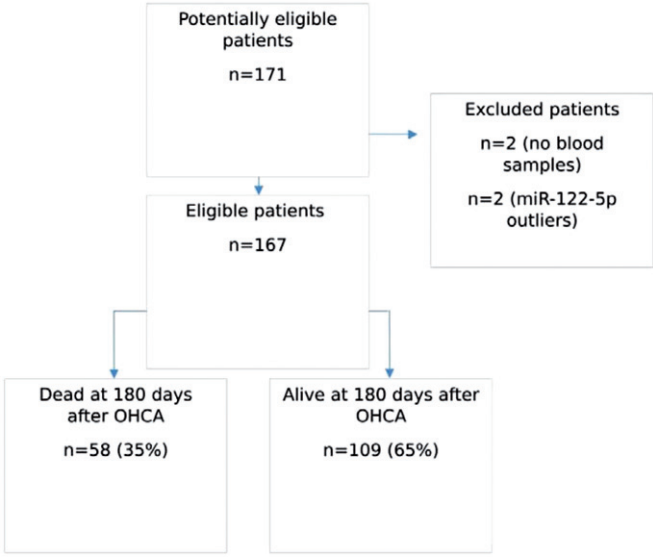

Figure 2. The study flow in the main trial.

Linear regression analyses

In the univariate regression analyses, miR-122-5p at admission was significantly correlated to lactate at admission ($\beta = 0.14$, $p < 0.01$), time to ROSC ($\beta = 0.03$, $p < 0.01$) and heart rate at admission ($\beta = 0.02$, $p < 0.001$). There were inverse relationships between miR-122-5p at admission and age ($\beta = -0.04$, $p < 0.05$), mean arterial pressure (MAP) at admission ($\beta = -0.02$, $p < 0.001$), bystander CPR ($\beta = -1.29$, $p < 0.01$) and left ventricular internal diameter end diastole (LVIDD) at admission ($\beta = -0.66$, $p < 0.05$). Other variables such as sex, creatinine, cardiac output at admission, central venous pressure at admission, left ventricular ejection fraction (LVEF) at admission, initial temperature and high-sensitivity Troponin-T were not related to miR-122-5p in the univariate analyses.

In the multiple linear regression analysis ($r^2 = 0.23$, $p < 0.001$), lactate at admission, bystander CPR and LVIDD at admission remained significantly associated with miR-122-5p at admission (Table 2).

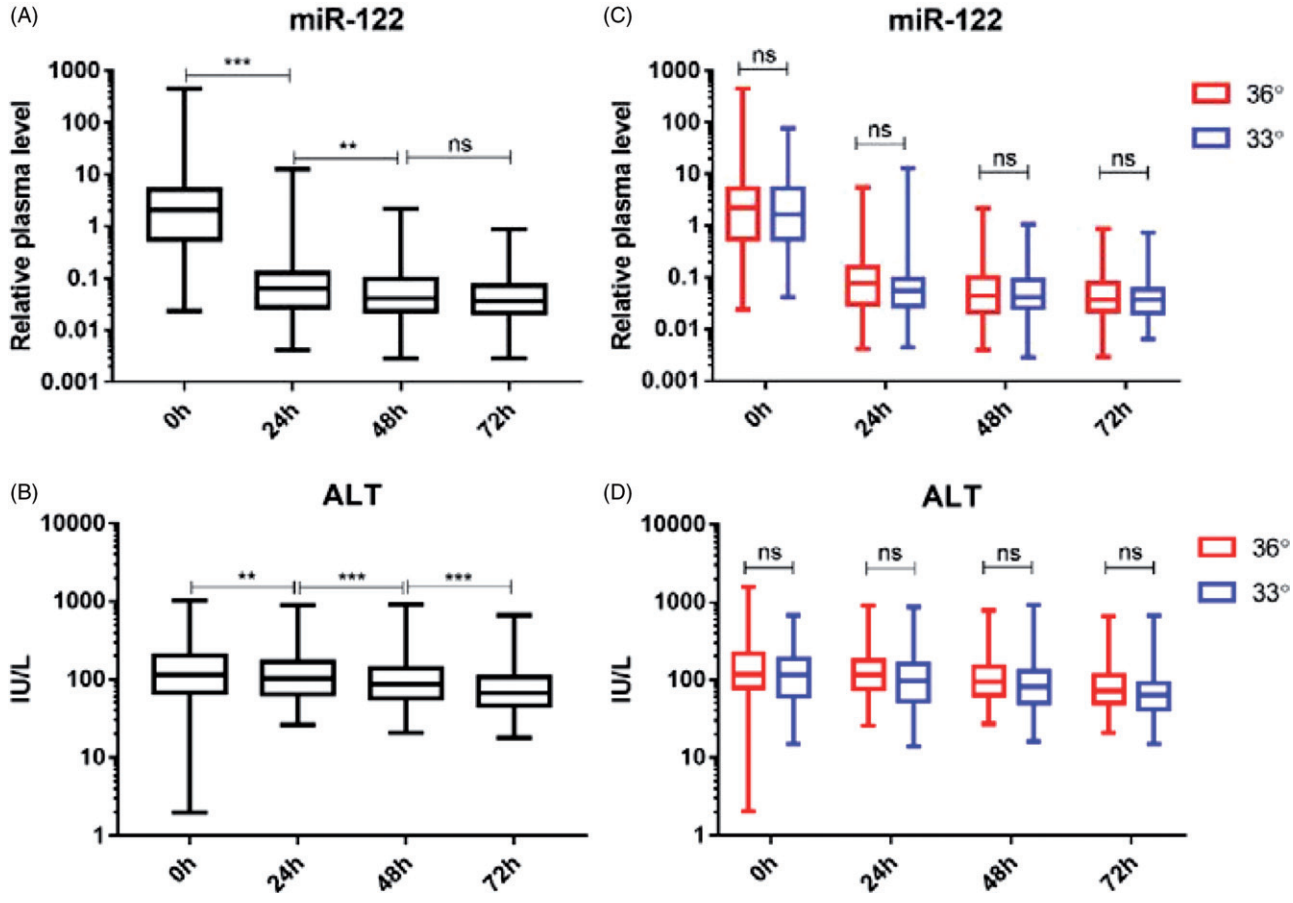

Figure 3. **(a, b)** In the main trial, the plasma miR-122-5p at admission was 57 fold/140-fold (median/mean) elevated compared to the 72 h time point ($p < 0.001$). **(c, d)** In the main trial, target temperature did not influence plasma levels of miR-122-5p or ALT. (Box and whisker plots are represented in the figures. The error bars represent the 95% CI, $^{**} = p \leq 0.01$, $^{***} = p \leq 0.001$, ns = not significant).

Table 2. Multiple linear regression analysis for prediction of plasma miR-122 at admission.

	β	95% CI	p-value
Lactate at admission (mmol/l)	0.130	0.03, 0.23	<0.01
LVIDD (cm)	−0.757	−1.25, −0.26	<0.01
Bystander CPR (yes)	−1.092	0.16, 2.04	<0.05
Age (years)	−0.031	−0.06, 0.00	0.06
MAP at admission (mm Hg)	−0.022	−0.05, 0.01	0.09
Creatinine at admission (mg/dl)	−0.004	−0.01, 0.00	0.11
Sex (male)	0.755	−0.36, 1.87	0.18
Time CA to ROSC (min)	0.006	−0.02, 0.03	0.65
Heart rate at admission (bpm)	−0.006	−0.03, 0.02	0.58
Shock at admission (yes)	0.064	−1.23, 1.36	0.92

Lactate at admission, bystander CPR and LVIDD at admission were independent predictors.
CI: confidence interval; MAP: mean arterial pressure; LVIDD: left ventricular internal diameter end diastole; CA: cardiac arrest; ROSC: return of spontaneous circulation; CPR: cardiopulmonary resuscitation.

miR-122-5p according to targeted temperature

Target temperature (33 °C vs 36 °C) was not associated with miR-122-5p at any time point (Figure 3(c)) and there were no interactions between target temperature and miR-122-5p.

miR-122-5p and shock at admission

Information about shock at admission was available for 167 patients (100%). Seventeen patients (10%) had shock at admission whereas 150 (90%) did not. There was a similar release pattern of miR-122-5p regardless of whether or not shock was present at admission. The median/mean plasma level of miR-122-5p at admission among patients with shock at admission was 1.8-fold/2.1-fold elevated compared to patients without shock, but this was not statistically significant ($p = 0.14$). In a logistic regression model including lactate at admission and time to ROSC, miR-122-5p at admission was not associated with shock at admission (OR: 1.04, 95% CI: 0.83–1.30, $p = 0.76$).

miR-122-5p and all-cause mortality

At 180 days after OHCA, 58 patients (35%) had died. With regard to survival status at 180 days, neither the release pattern of miR-122-5p nor the miR-122-5p levels at any time point differed between the groups. In a logistic regression analysis, miR-122-5p at admission was not associated with all-cause mortality ($p = 0.35$) (Table 3).

Levels of miR-122-5p at admission could not discriminate between cerebral (67% of deaths, $n = 39$) and cardiovascular/multi-organ failure (29% of deaths, $n = 17$), causes of death (p=ns).

miR-122-5p and liver enzymes

The release pattern of ALT is shown in Figure 3(b). ALT did not differ between the outcome groups (131 IU/l vs 144 IU/l for survivors vs non survivors, respectively, p=ns) or between different causes of death (140 IU/l vs 144 IU/l for cerebral vs cardiovascular/multi-organ failure, p=ns). miR-122-5p at admission was significantly correlated with ALT at all time-points (at admission $r = 0.59$ ($p < 0.001$), at 24 h $r = 0.59$ ($p < 0.001$), at 48 h $r = 0.57$ ($p < 0.001$) and at 72 h $r = 0.55$ ($p < 0.001$)). miR-122-5p (log2) at admission was linearly related to ALT ($\beta = 0.32$, $p < 0.001$) in the univariate analysis (Figure 4). In the multivariable regression analysis ($r^2 = 0.44$, $p < 0.001$) including, creatinine at admission, lactate at admission, bystander CPR, shock at admission, age and sex, miR-122-5p at admission remained independently associated with ALT at admission ($\beta = 0.29$, 95% CI: 0.21–0.37, $p < 0.001$). There were no significant associations between ALT at admission and invasive hemodynamic parameters or between ALT at admission and temperature assignment (33 °C vs 36 °C) at any time point (Figure 3(d)).

Table 3. Logistic regression analysis with clinical variables to predict all-cause mortality at 180 days after OHCA.

	OR	95% CI	p-value
Age (years)	1.08	1.04, 1.13	<0.001
Time CA to ROSC (min)	1.06	1.02, 1.09	<0.01
First rhythm (VT/VF)	0.18	0.05, 0.64	<0.01
miR-122 at admission (log2)	1.12	0.89, 1.40	0.35
Target temperature (33 °C)	0.74	0.33, 1.70	0.48
Lactate at admission (mmol/l)	1.02	0.93, 1.11	0.69
Bystander CPR (yes)	1.08	0.40, 2.94	0.88

miR-122 at admission was not an independent predictor of all-cause mortality.
CI: confidence interval; CA: cardiac arrest; ROSC: return of spontaneous circulation; VT: ventricular tachycardia; VF: ventricular fibrillation; CPR: cardiopulmonary resuscitation.

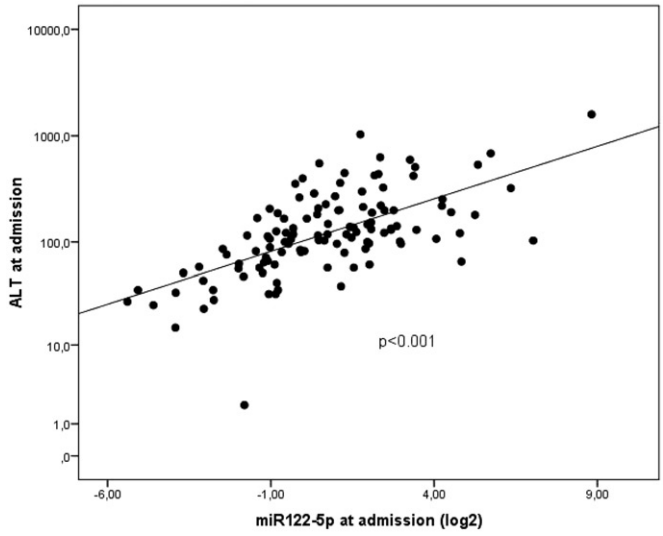

Figure 4. At admission, miR-122 was linearly related to ALT. In the linear multiple regression model, miR-122 at admission was an independent predictor of ALT at admission ($\beta = 0.29$, 95% CI: 0.21–0.37, $p < 0.001$).

Discussion

Treatment of patients that remain unconscious after OHCA is challenging and biomarkers for early detection of organ dysfunction are needed. In this study of unconscious patients with OHCA surviving to temperature management, the liver-specific miR-122-5p had a very rapid release pattern and was already 400-fold higher than levels in controls at admission. After reaching the peak of admission, miR-122-5p levels decreased rapidly before plateauing at 48 h. miR-122-5p at admission correlated to lactate, bystander CPR and LVIDD,

but was not associated with all-cause mortality at 180 days or shock at admission.

The acutely increased levels of plasma miR-122-5p at admission harmonize with findings by Wander *et al.* (2016), who reported an elevated plasma miR-122 already during resuscitation from ventricular fibrillation compared to controls. Plasma miR-122 during resuscitation was also higher among patients surviving to discharge compared to those who died in the field. However, resuscitation times were not available which might confound the survival analysis. In contrast, Devaux *et al.* (2017) described an independent association between lower levels of miR-122-5p at 48 h after OHCA and a poor outcome. One might speculate that lower levels of miR-122-5p at 48 h among patients with poor prognosis represent a rebound phenomenon after high initial plasma levels. However, miR-122-5p at admission was not associated with all-cause mortality in our study.

In the multiple linear regression model, lactate at admission was independently associated with miR-122-5p at admission. This association might reflect a reduced capability of the liver to metabolise lactate through the Cori cycle (Jansen *et al.* 2009). However, lactate is a surrogate marker of hypoperfusion and closely relates to multiple organ dysfunction and shock (Jansen *et al.* 2009). Our results are in line with previous findings in a pig cardiogenic shock model, where miR-122-5p increased rapidly after induction of shock and was correlated to pH and MAP during chock (Andersson *et al.* 2012). We did not observe an association between MAP and miR-122-5p at admission but MAP is an inadequate marker of circulatory failure due to the common use of vasopressors in the post cardiac arrest setting. Due to the acute increase of miR-122-5p during the first hours after OHCA and its association with lactate at admission, one could speculate that miR-122-5p might be a hyper-acute marker of circulatory collapse and a very early marker of liver dysfunction. On the other hand, patients with shock at admission in the present study had only a non-significant increase of miR-122-5p compared to patients without shock ($p = 0.14$) and the logistic regression model could not detect any association between miR-122-5p at admission and shock at admission. However, since only 17 patients (10%) had shock at admission this might be a type II error and larger studies are needed to further investigate miR-122-5p as a marker of shock.

The association between miR-122-5p and bystander CPR indicates that some of the release of miR-122-5p might be secondary to traumatic injury. Moreover, bystander CPR is often performed by laymen which might increase the risk of inadvertent compression of the liver (Bossaert and Van Hoeyweghen 1989). The inverse association between miR-122-5p and LVIDD is not intuitive. Increased LVIDD is associated with cardiac preload, cardiac remodelling and reduced LVEF in systolic heart failure (Wong *et al.* 2004). Previous known heart failure was uncommon in the cohort (4%) and there was no differences in LVIDD between the outcome groups. The negative association between miR-122-5p and LVIDD therefore remains unclear.

Our study has some strengths. First, the study includes a relative large population and no patients were lost to follow up. Second, all-cause mortality was used as endpoint. Third, in the pilot study plasma miR-122-5 levels among patients were compared to matched controls.

Limitations to the study includes that only one miRNA, miR-122-5p, was evaluated. However, miR-122-5p was chosen based on a literature review. The study was also underpowered to assess the correlation between plasma levels of miR-122-5p and subgroups, such as shock status at admission and causes of death.

Conclusions

The liver-specific miR-122-5p in plasma seems to be a hyper-acute biomarker after cardiac arrest and is 400-fold elevated at admission after OHCA compared to controls. miR-122-5p at admission is not associated with all-cause mortality or presence of shock at admission . A targeted temperature of 33 °C compared to 36 °C did not affect miR-122-5p levels. miR-122-5p at admission was independently associated with elevated lactate levels, LVIDD and bystander CPR.

Disclosure statement

No potential conflict of interest was reported by the authors.

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